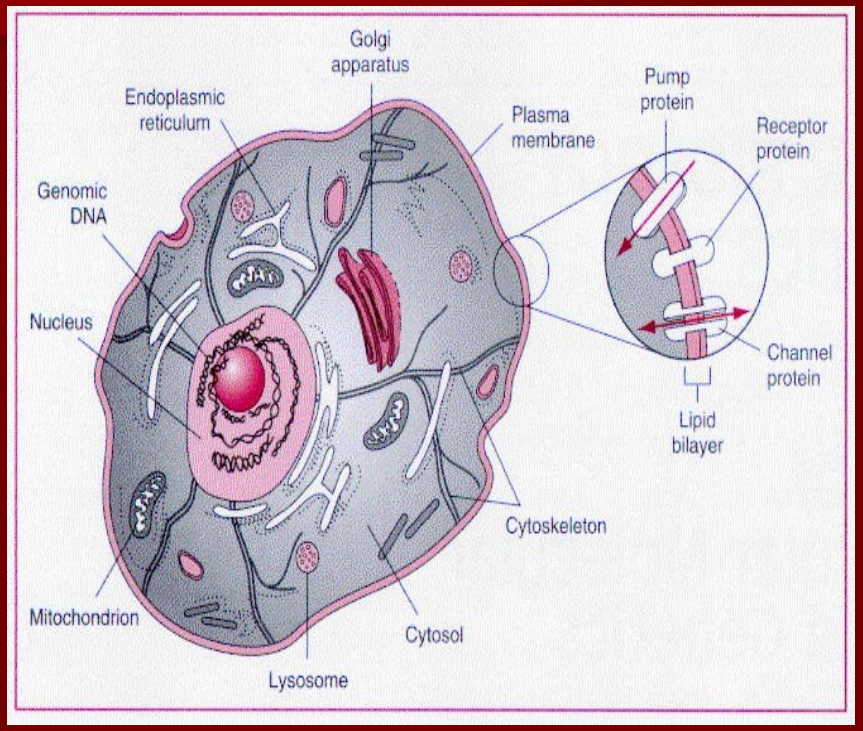
ARRHYTHMIAS

BASIC MECHANISMS AND TREATMENT

Introduction

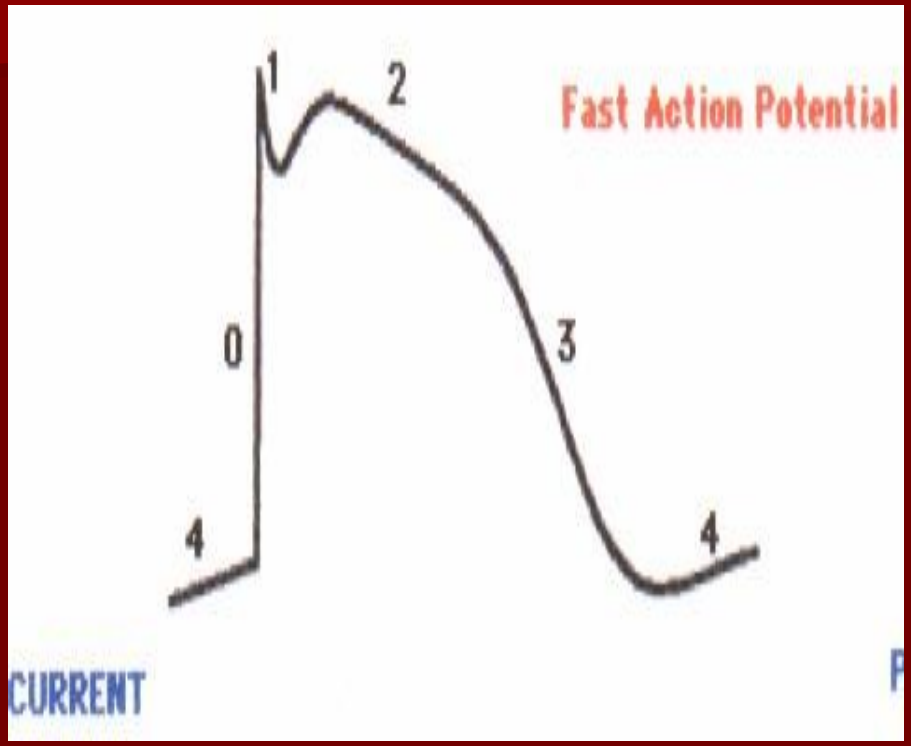
- Cellular structure
- Normal electrophysiology
- Arrhythmogenesis
- Antiarrhythmic agents
- Examples

Cellular Structure



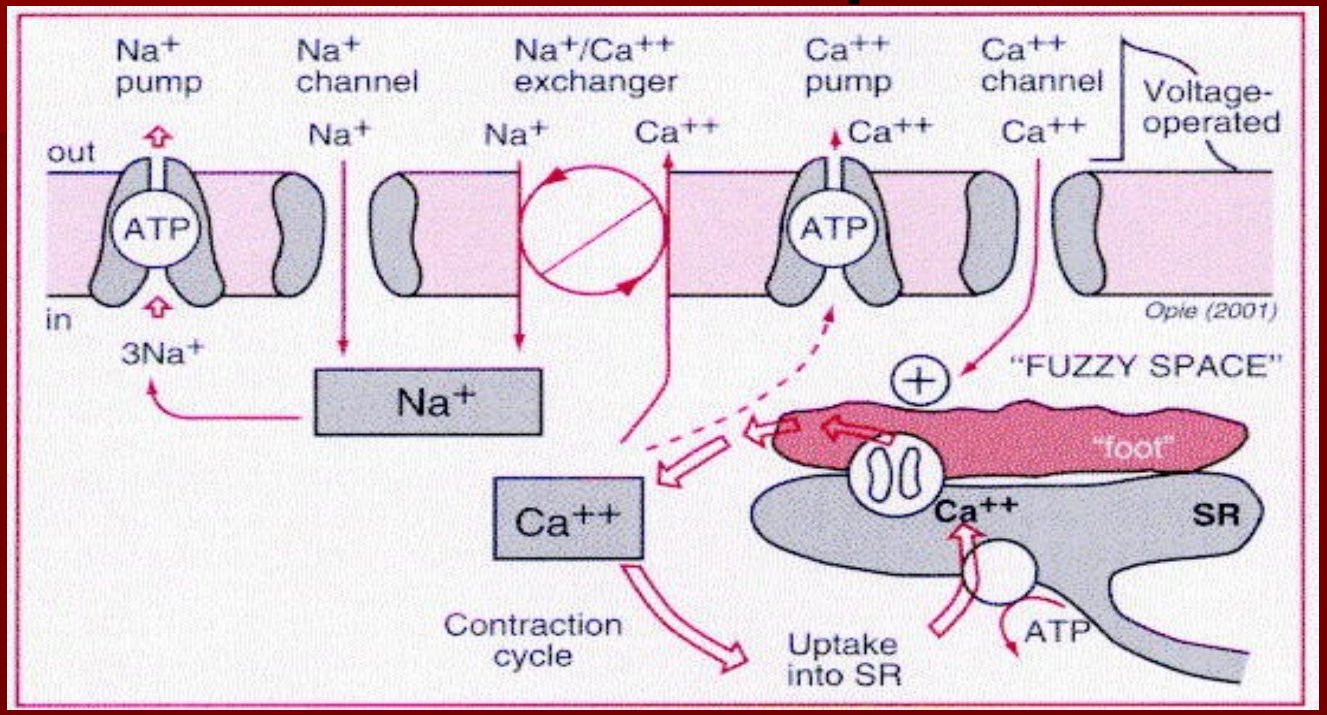
- Phospholipid bilayer
- Impermeable
- Spanning proteins
- Channels, receptors and pumps

Cardiac Action Potential



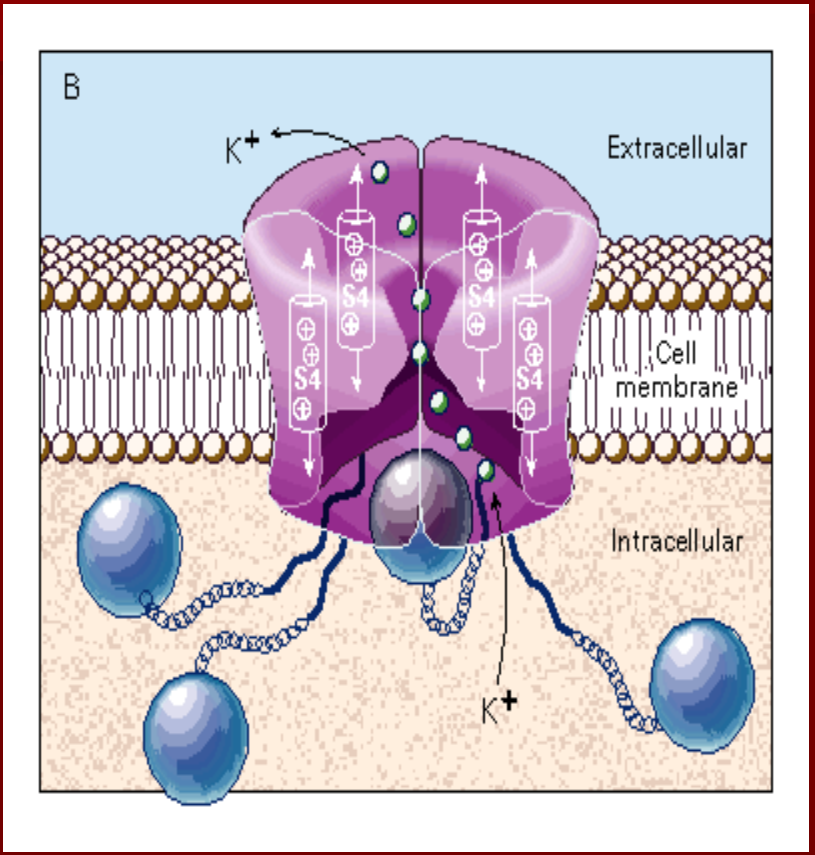
- Result of spontaneous depolarization or stimulus to threshold potential
- Complex interplay of ion channels, voltage and time

Ion Pumps



- Na^+/K^+ ATPase, 3 Na^+ out 2 K^+ in
- 30% of cellular energy

Ion Channels

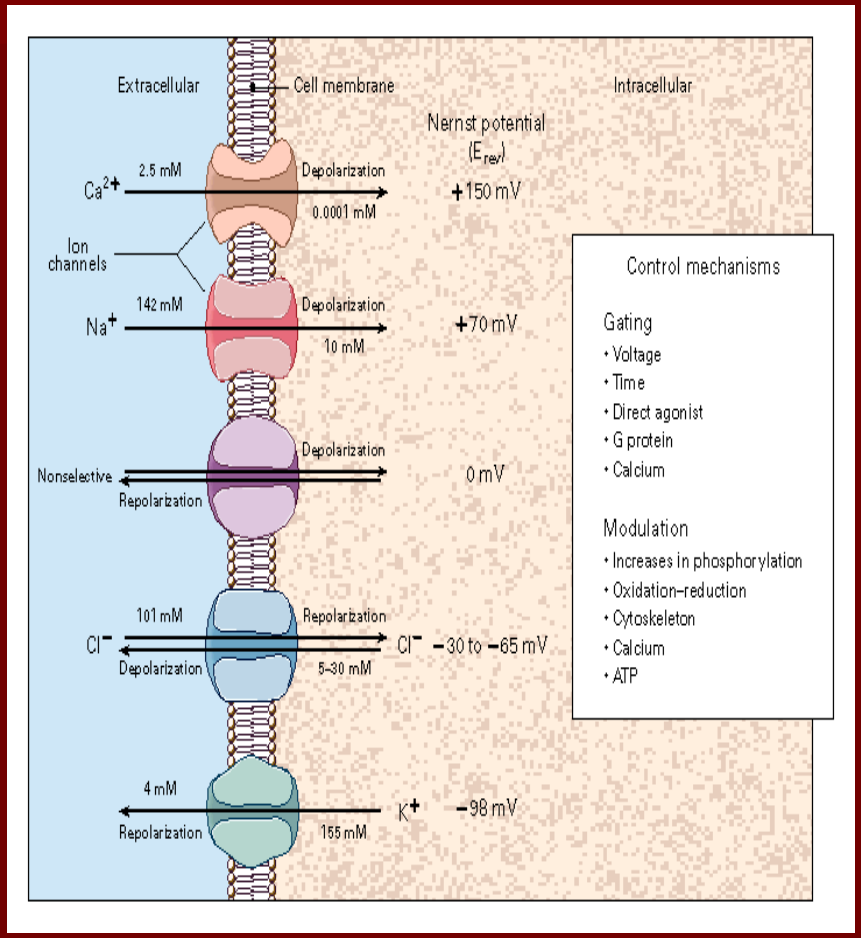


- Macromolecular protein tunnels
- Highly selective to particular ion
- Respond to various modifiers (voltage, time, other ion concentrations)
- Conformational changes
- Act as switches to energy created by pumps

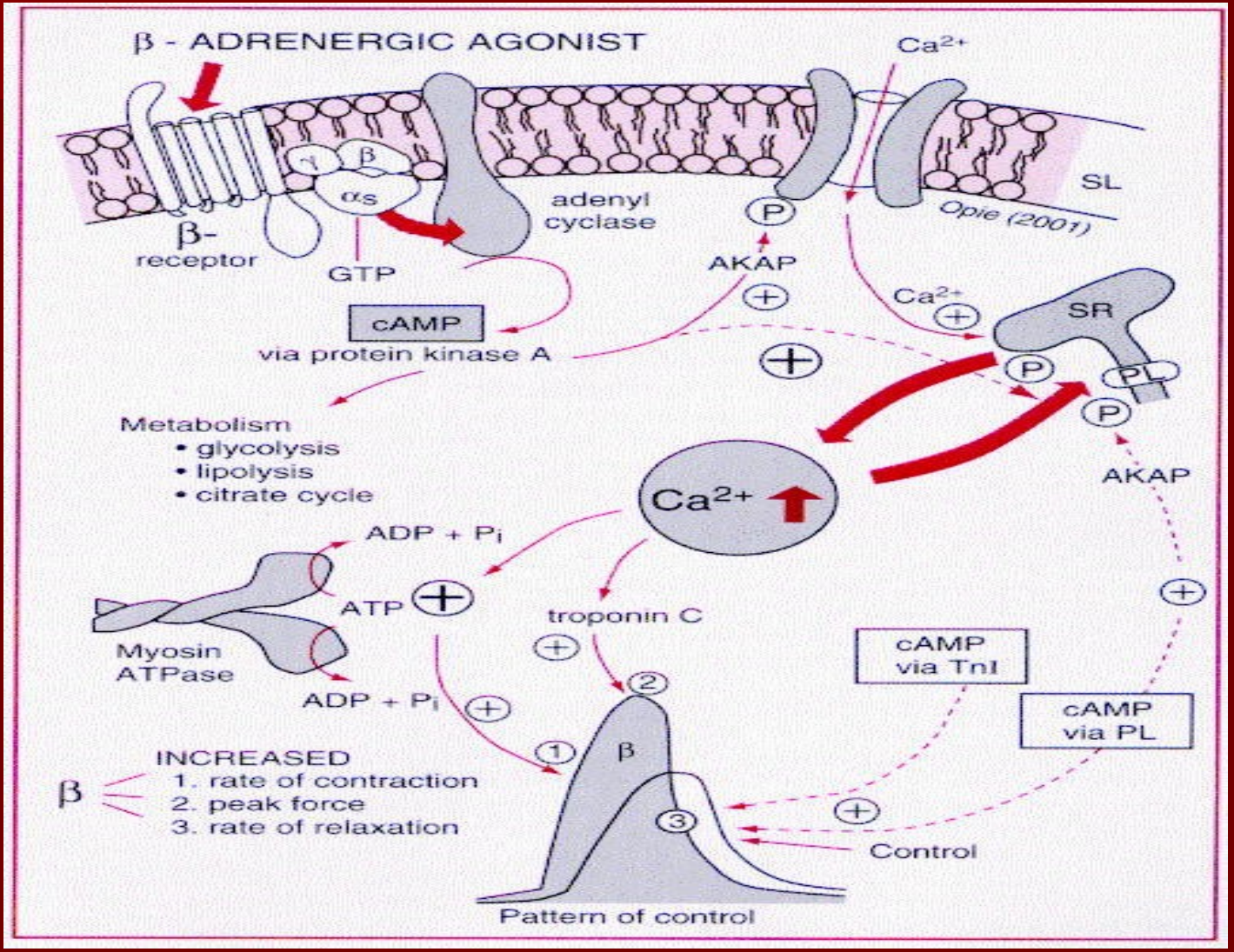
Resting Membrane Potential

- Intracellular K^+, 140 mM/L, extracelluar 4 mM/L
- Intracelluar Na^+, 10-15mM/L, extracelluar 140 mM/L
- At rest K^+ channel is open, others closed

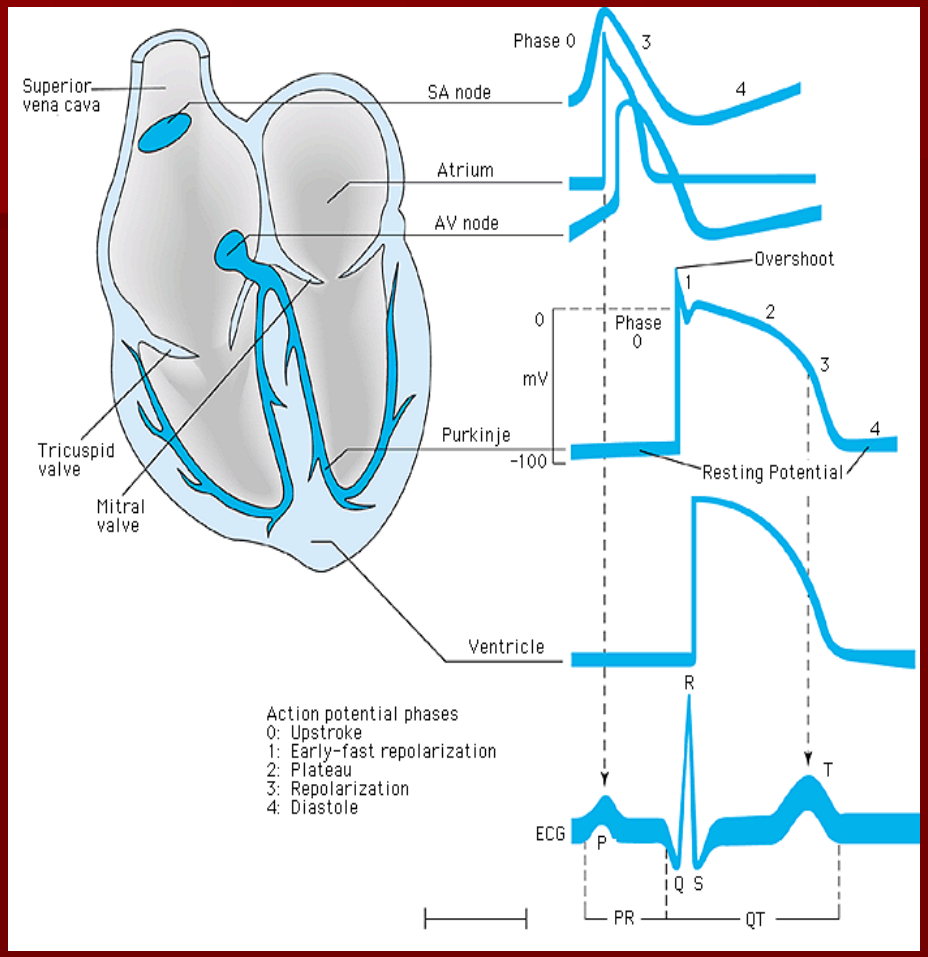
$$E_K = 61 \times \log(K^+_e / K^+_i)$$

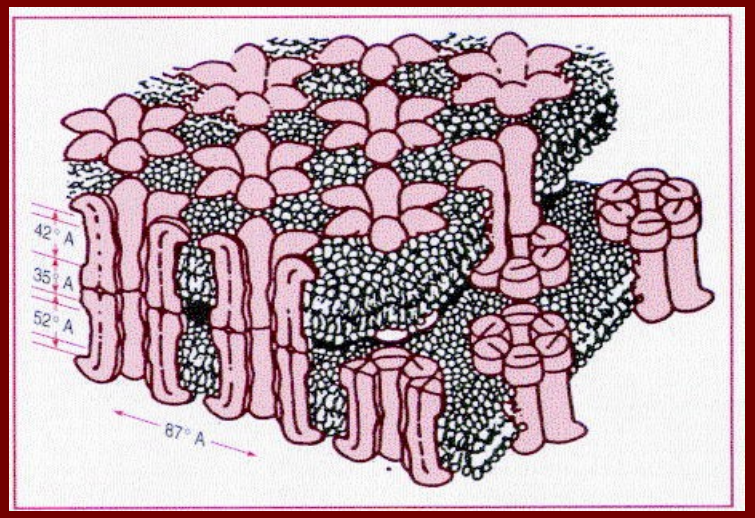


Receptors


β - ADRENERGIC AGONIST
Ca2+
SL
Opie (2001)
β-
receptor
GTP
adenyl
cyclase
AKAP
cAMP
via protein kinase A
Ca2+
SR
PL
Metabolism
• glycolysis
• lipolysis
• citrate cycle
Ca2+
AKAP
ADP + Pi
ATP
Myosin
ATPase
troponin C
cAMP
via TnI
cAMP
via PL
ADP + Pi
INCREASED
1. rate of contraction
2. peak force
3. rate of relaxation
β
Control
Pattern of control

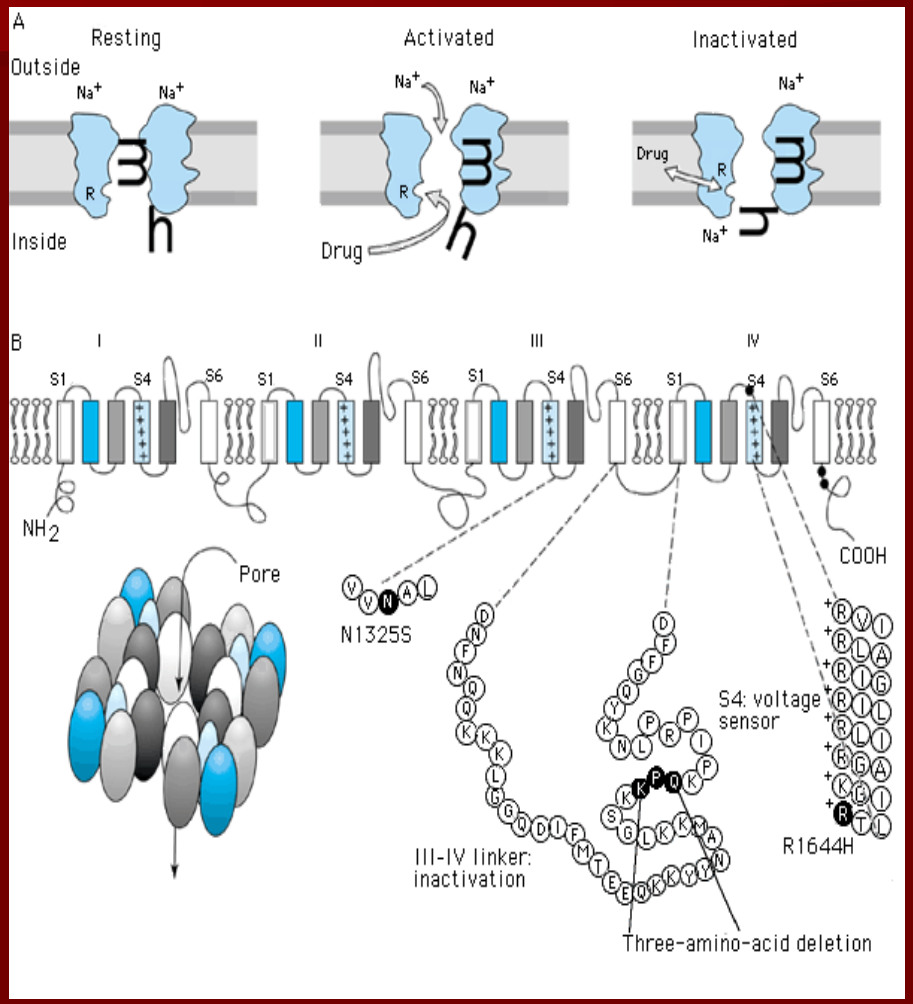
Cardiac Action Potential





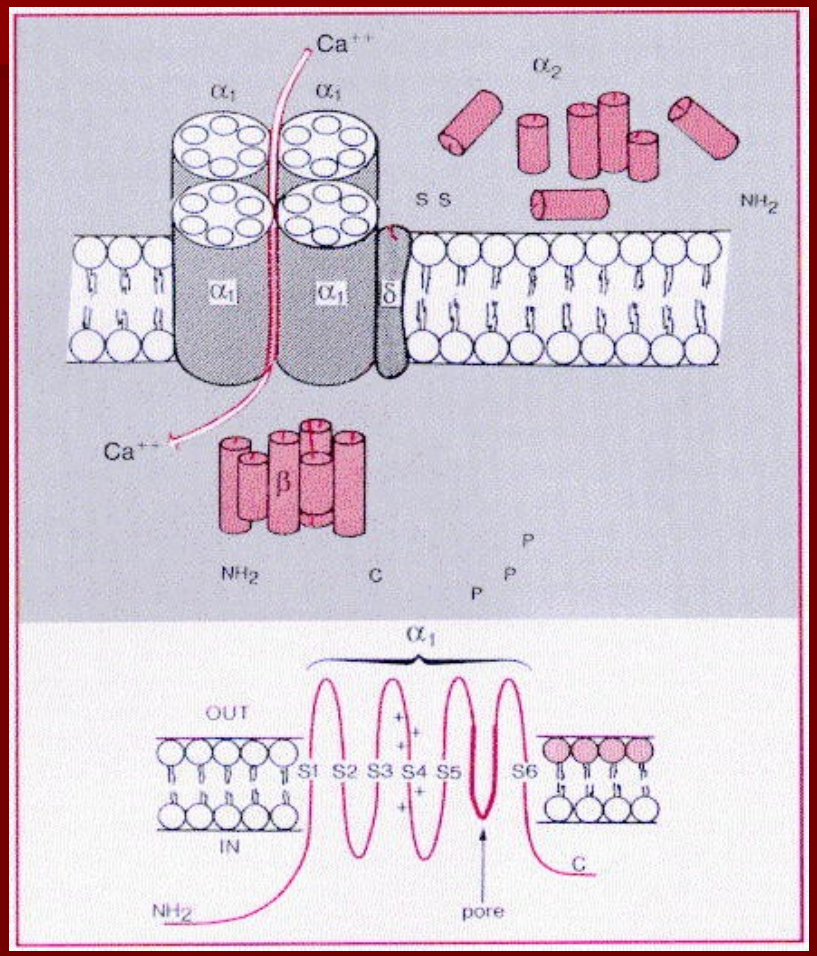
- Cell specific
- Spread dependent on reaching threshold
- Facilitated through ion movement via gap junctions

Na^+ channels



- Phase 0 in fast response (ventricular atrial and Purkinje) tissue
- Voltage and time dependent
- 3 states
- Class I agents

Ca^{2+} Channels

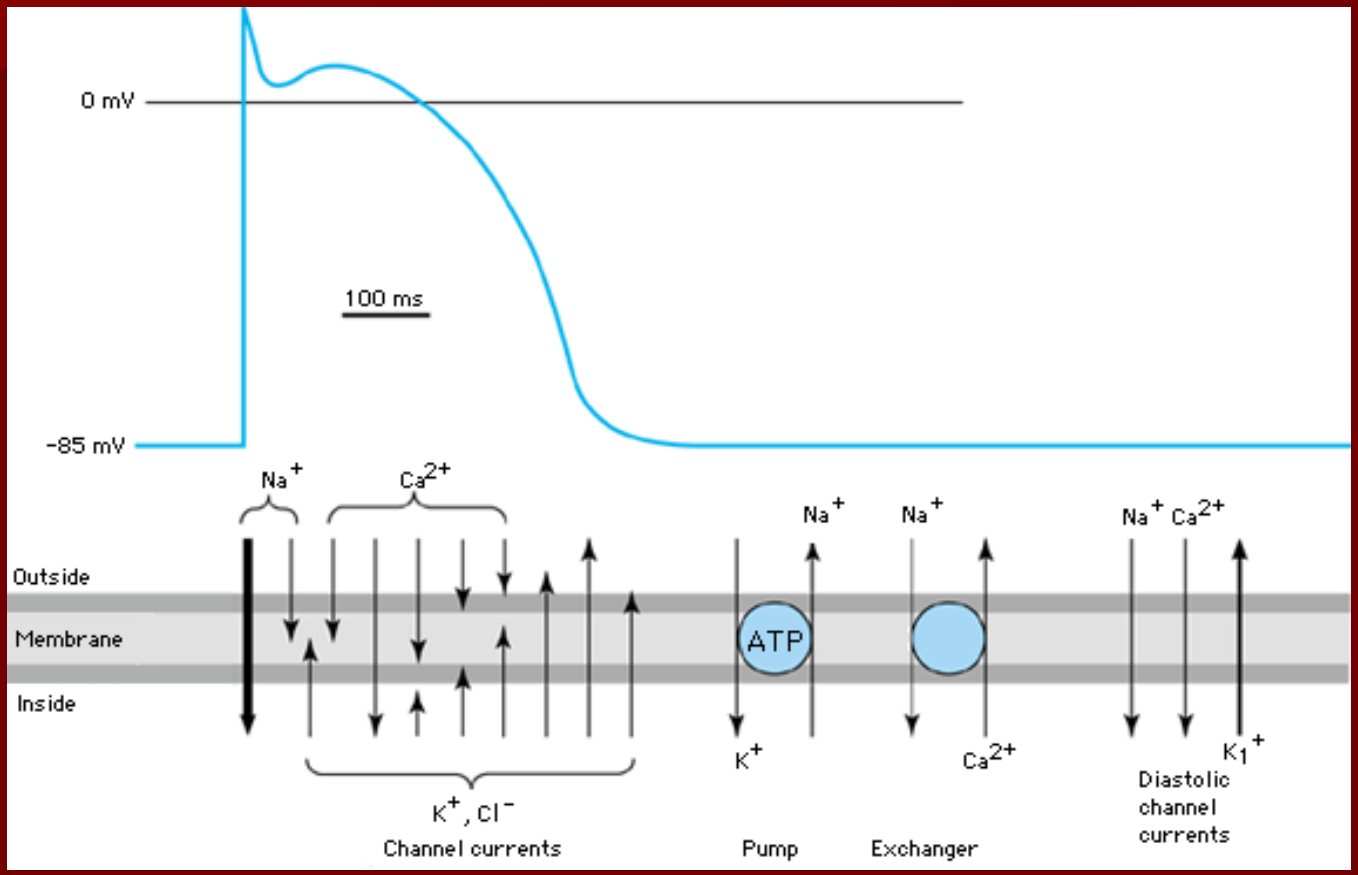


- T type (transient, tiny), pacemaker
- L type (long-lasting) dominant depolarizing current (phase 0) of SA and AV node, plateau (phase 2) of ventricle, atrium
- L type, target of Ca^{2+} channel blockers

K^+ Channels

- I_{KI} – voltage dependent, generates RMP
- I_K – responsible for repolarization, 2 components, I_{Kr} (rapid), I_{Ks} (slow)
- I_{TO} – transient outward, generates phase I
- I_{Kach}- acetylcholine/adenosine sensitive, causes hyperpolarization and APD shortening
- I_{KATP}- shortens APD when ATP scarce

Cardiac Action Potential



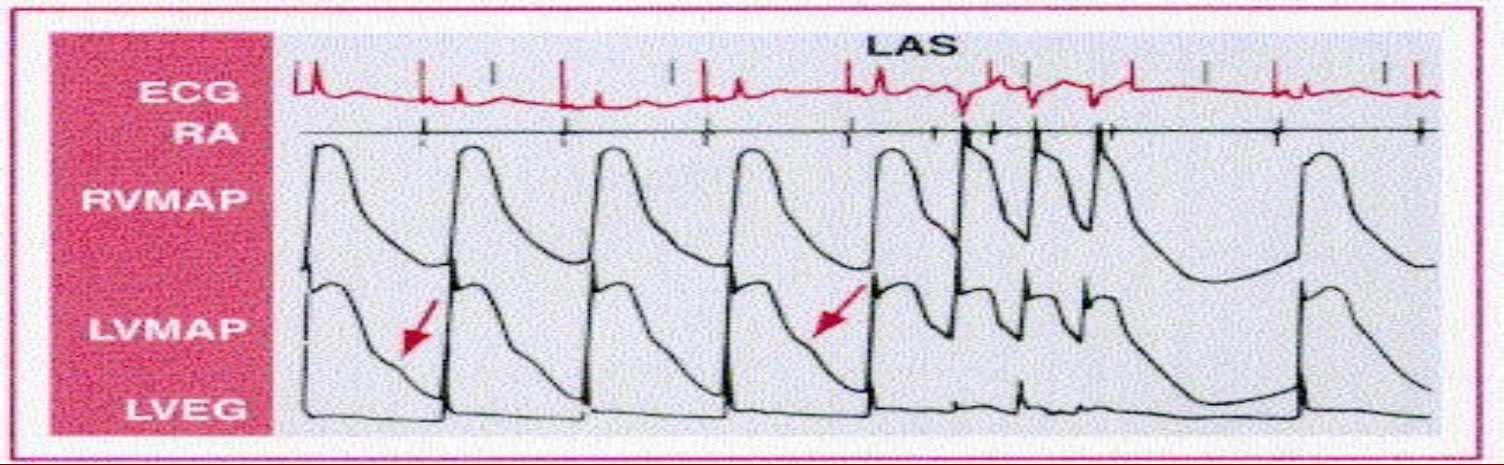
Arrhythmogenesis

- Disorders of impulse formation and disorders of impulse conduction
- Clinically difficult to distinguish
- Initiated by one mechanism, perpetuated by another

Disorders of Impulse Formation

- Generally occur on a cellular level
- Divided into abnormal automaticity and triggered activity
- SA, AV node and His-purkinje cells demonstrate automaticity (phase 4)
- Relative depolarization (ischemia), other cells may demonstrate
- Examples, atrial tach, post MI ventricular arrhythmias

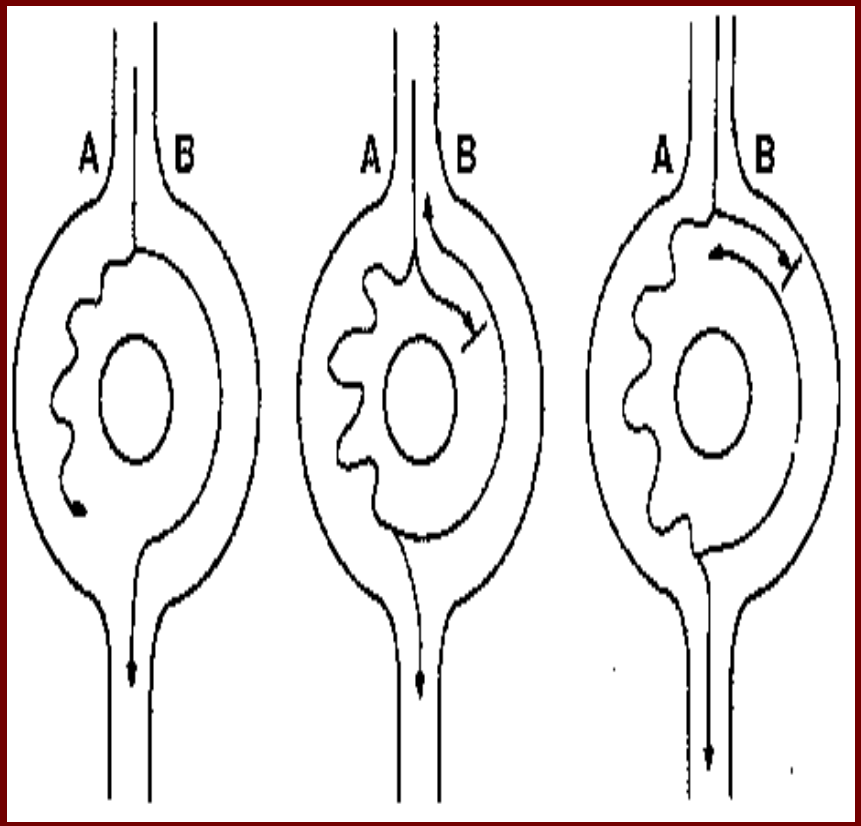
Disorders of Impulse Formation



- Triggered activity – oscillations in membrane potential induced by a prior action potential
- Dig toxicity (phase 4 DAD's), congenital and acquired LQTS (phase 3 EAD's)

Disorders of Impulse Conduction

- Occur on a multicellular or structural level
- Failure to conduct (AV Block, Sinus exit block)
- Reentry 3 conditions – obstacle to conduction delayed conduction unidirectional block
- AVNRT, AVRT, Afib, flutter, scar mediated VT



Antiarrhythmic Targets

- Decrease abnormal automaticity
- Prevent triggered activity
- Modify conduction
- Prolong refractoriness

Antiarrhythmics Vaughn-Williams Classification

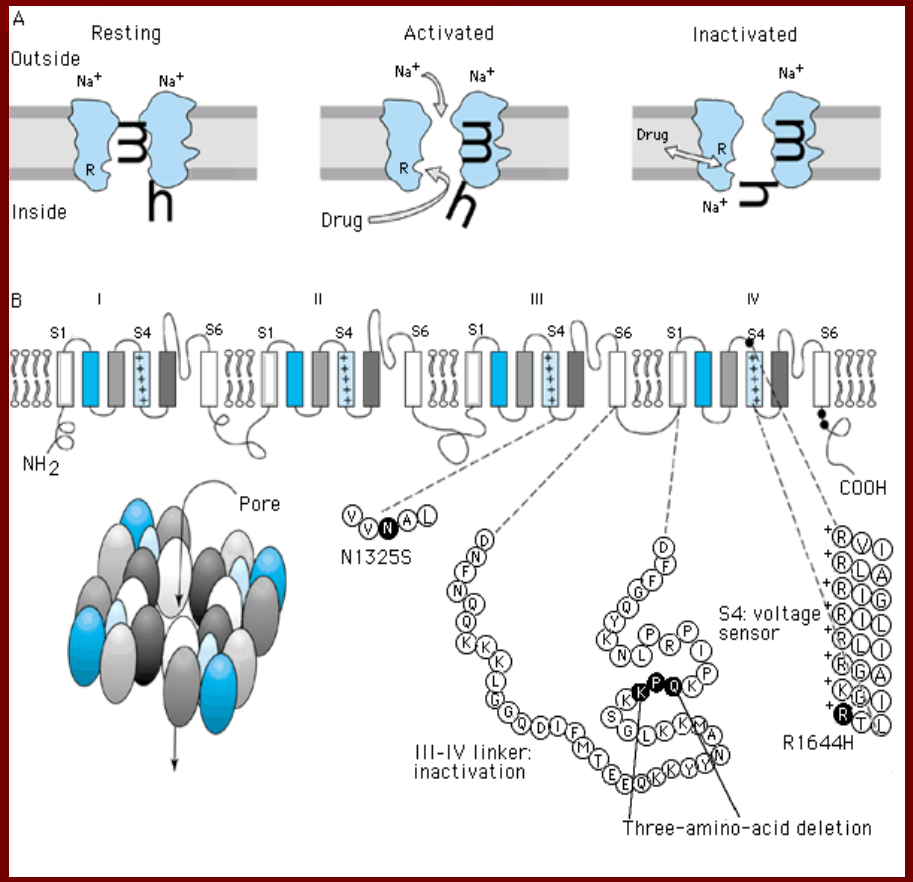
- Class I – Na^{+} channel blockers
  - IA – Procainamide, Disopyramide, Quinidine
  - IB – Lidocaine, Mexiletine, Tocainide
  - IC – Flecainide, Propafenone
- Class II – Beta-blockers
- Class III – K^{+} channel blockers
  - Sotalol, Ibutilide, Amiodarone, Dofetilide
- Class IV – Ca^{2+} channel blockers

Class I
Na^+ channel Blockers

- Slow conduction (IC>IA>IB)
- Useful for reentrant rhythms in Na^+ dependent tissue
- Depress automaticity
- IC's prolong refractoriness without affecting APD
- IA's block several K^+ channels, inc APD

Class I Na^+ Channel Blockers

- Display use dependence
- Effect of ischemia
- Proarrhythmia risk slow conduction prolong QT
- IC's increase mortality in ischemic CM
- Contraindicated

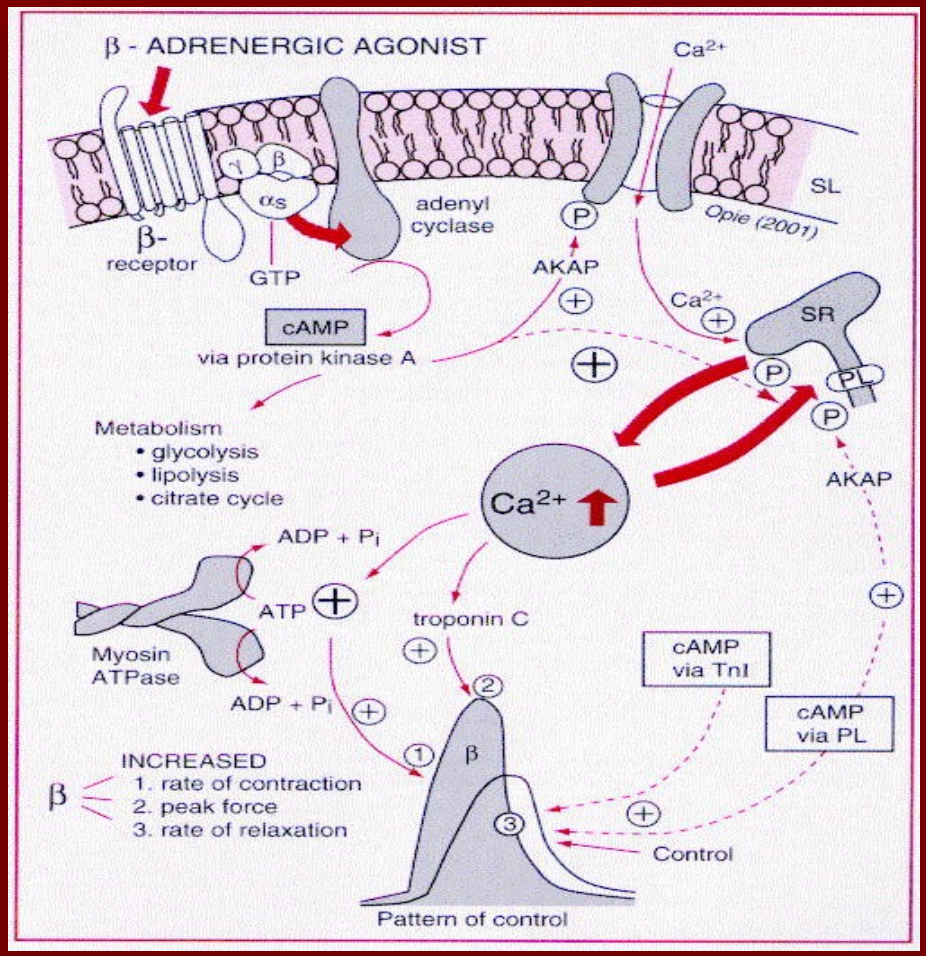


Class I
Na^+ Channel Blockers

- IA/IC, atrial fib/flutter or atrial tach with normal LV/no ischemia
- IB no significant effect on atrial tissue
- Lidocaine indicated for VF/VT

Class II Beta-Blockers

- Reversibly bind to beta-receptors
- Decrease pacemaker current, increase threshold (dec automaticity)
- Indirect inhibition of L type Ca^{2+} channels (slow conduction in AVN)

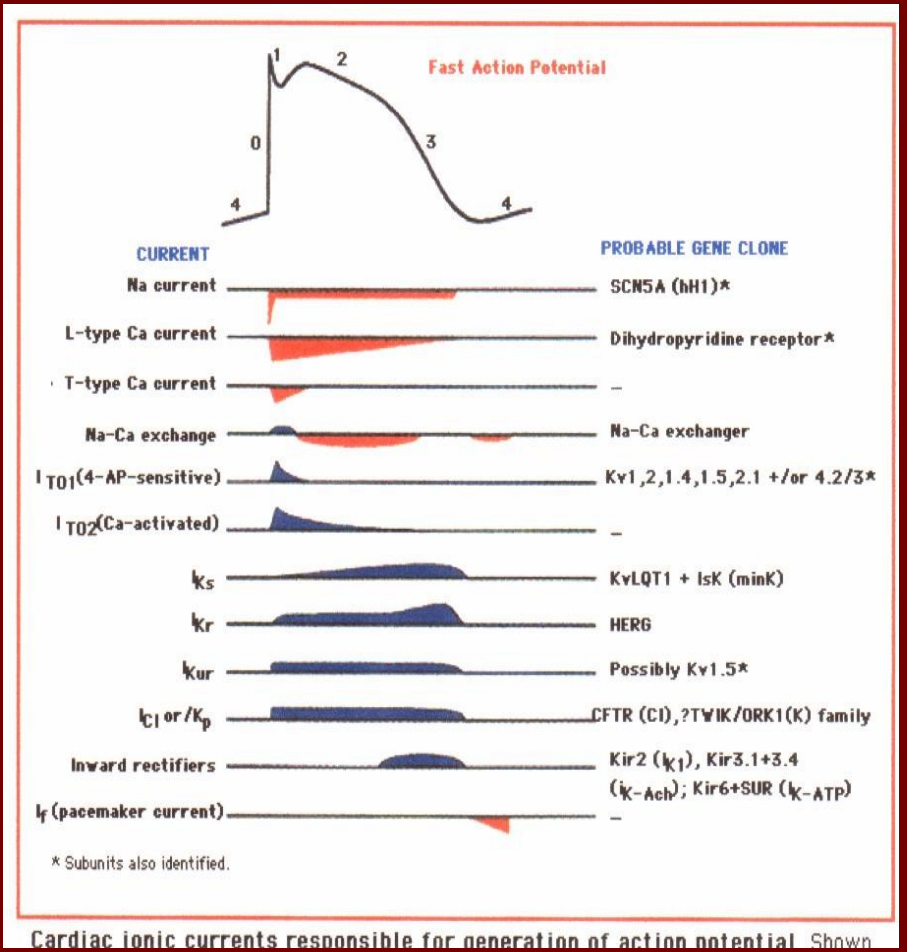


Class II
Beta-Blockers

- Hyperadrenergic states
  reduce SCD risk post MI, CHF
  automatic rhythms (atrial tach)
- Reentrant rhythms using AVN
  AVRT, AVNRT
- Slow ventricular rate in atrial fibrillation
- No ventricular proarrhythmia
- Bradycardia/heart block can limit use

Class III
K^+ Channel Blockers

- Sotalol, Ibutilide, Dofetilde inhibit I_{Kr}
- Amiodarone inhibits I_{Kr} and I_{Ks}
- Markedly prolong APD
- Sotalol beta-blocker
- Amio class I, II, IV



Cardiac ionic currents responsible for generation of action potential. Shown

Class III
K^+ Channel Blockers

- I_{Kr} blockers display reverse use dependence
- Torsade risk up to 8%!
- Variant of LQTS
- Amio no significant risk of ventricular proarrhythmia
- Possibly mediated by I_{Ks} block

Class III
K^+ Channel Blockers

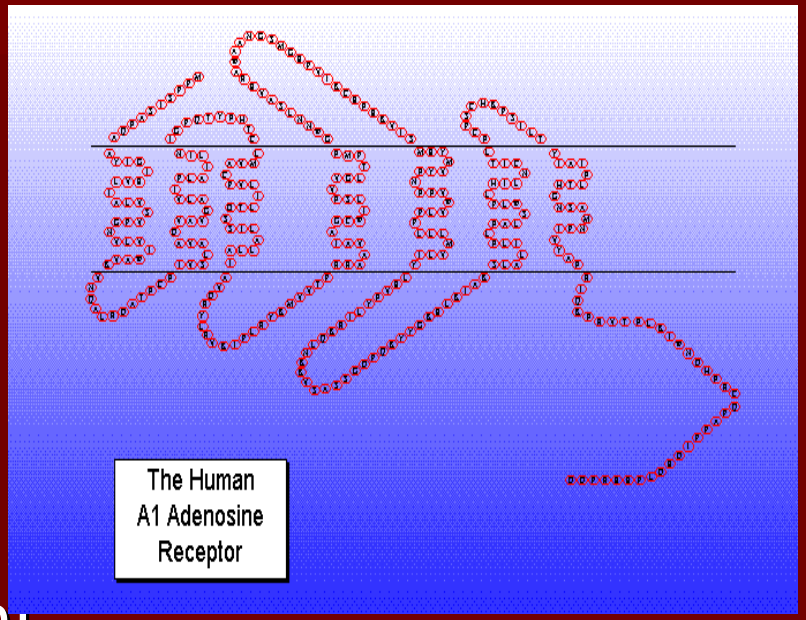
- I_{Kr} blockers, wide variety of reentrant arrhythmias (afib, atrial flutter)
- Avoided in presence of LVH and poor LV function
- Sotalol reduces ICD shocks
- Amio broadest range of indications
- Limited by bradycardia/AVN block and extracardiac effects

Class IV Ca^{2+} Channel Blockers

- Inhibit L type Ca^{2+} channels
- Slow phase 4 (reduce automaticity) in SA and AV nodes
- Slow conduction/prolong refractoriness in AV node
- Useful for PSVT, slow ventricular rate in atrial fibrillation, rare form of VT
- Limited by bradycardia/AVN block
- Mortality neutral, no ventricular proarrhythmia

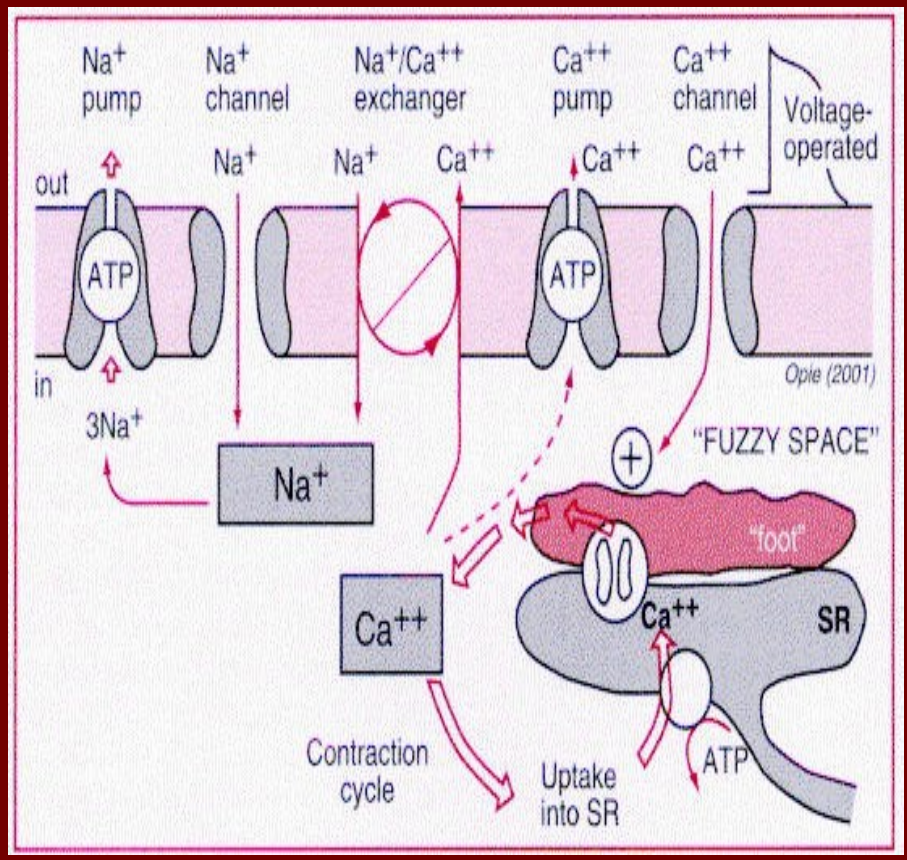
Adenosine

- Endogenous nucleoside
- Adenosine (A_1) receptor agonist
- Activates outward I_{KAdo} K^+ current causing hyperpolarization
- Inhibits pacemaker current
- Results in profound slowing of sinus rate, AV nodal block
- Agent of choice for PSVT

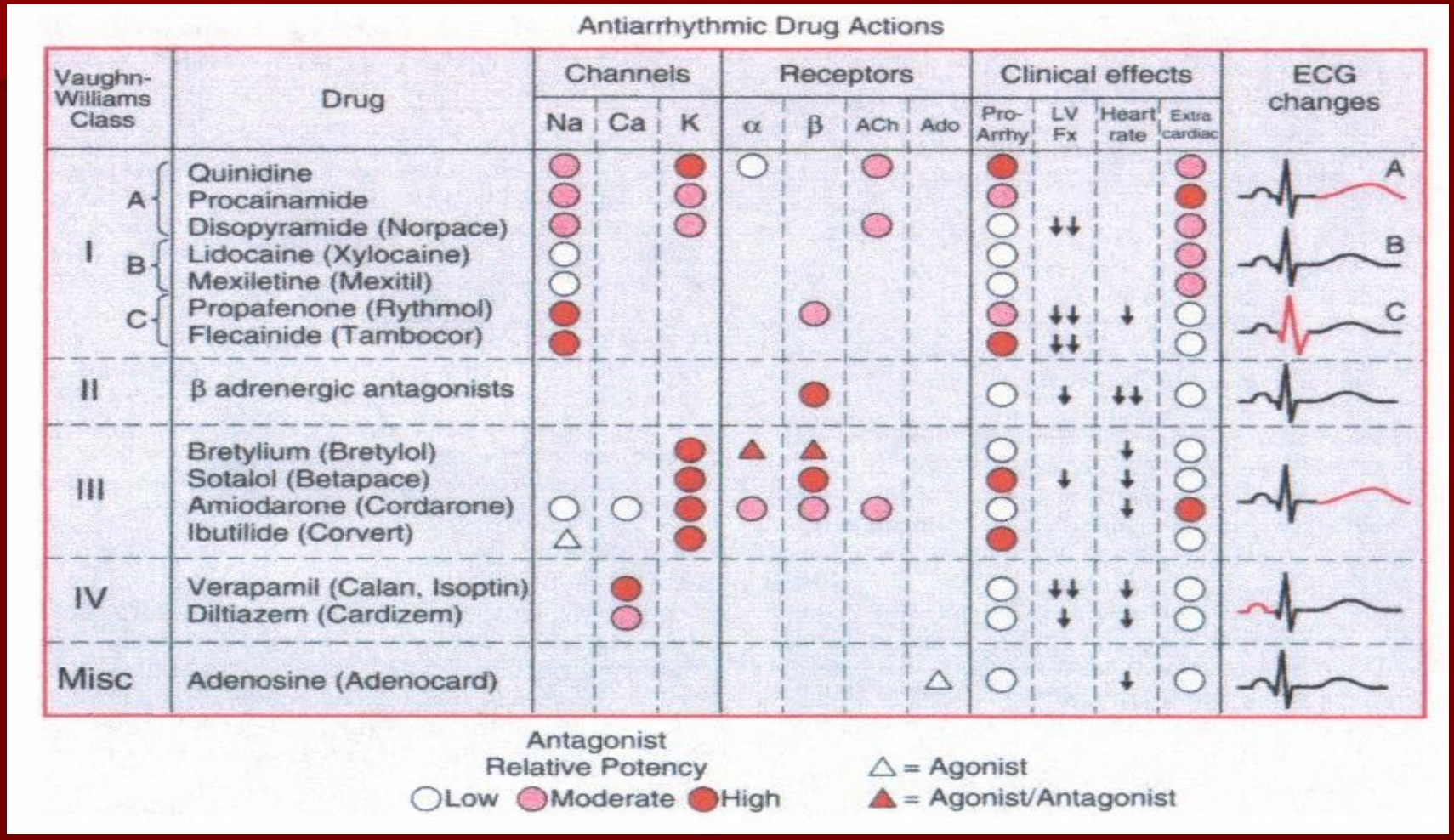


Digoxin

- Inhibits Na^+/K^+ pump
- Increases intracellular Ca^{2+}
- Increases Vagal tone
- Atrial fibrillation in presence of CHF
- PSVT in pregnancy
- DAD's
- Mortality neutral

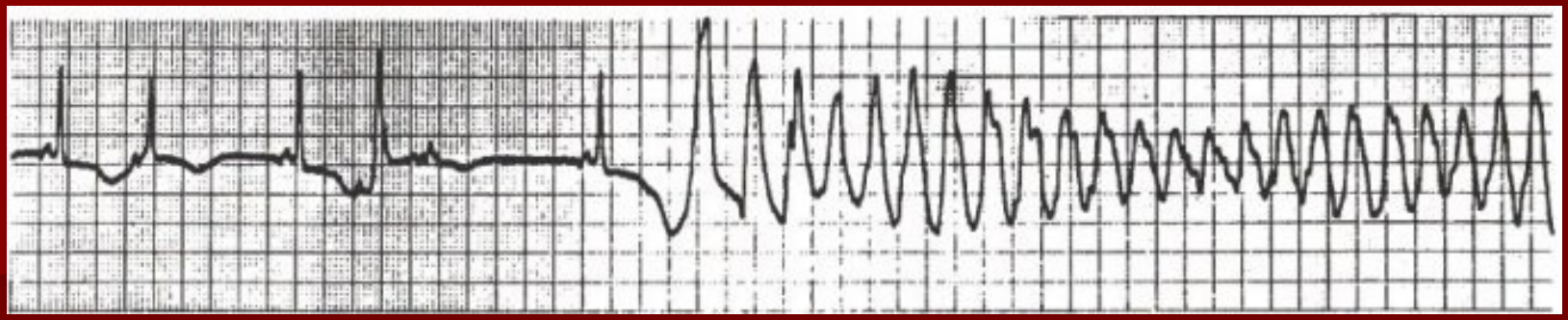


Antiarrhythmics
Sicilian Gambit

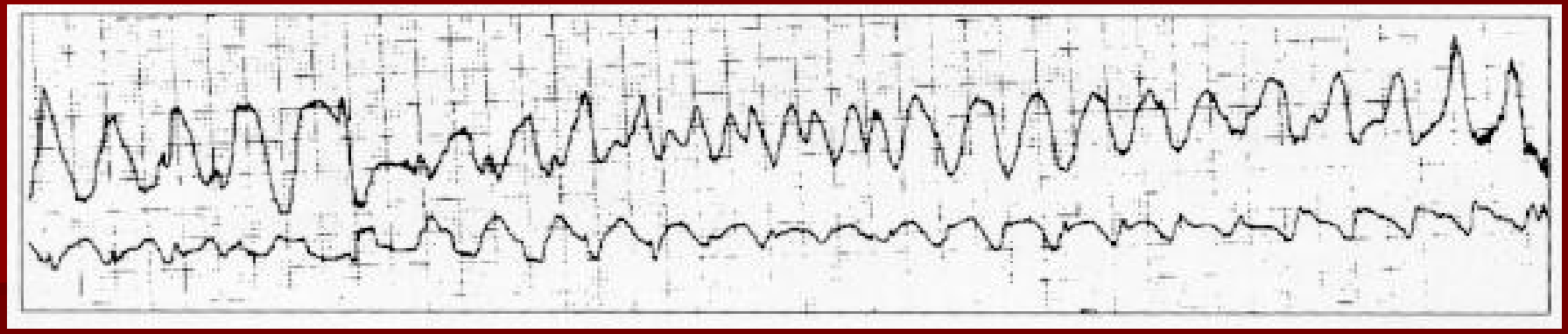


Arrhythmia Examples

- What Rhythm
- Mechanism
- Treatment

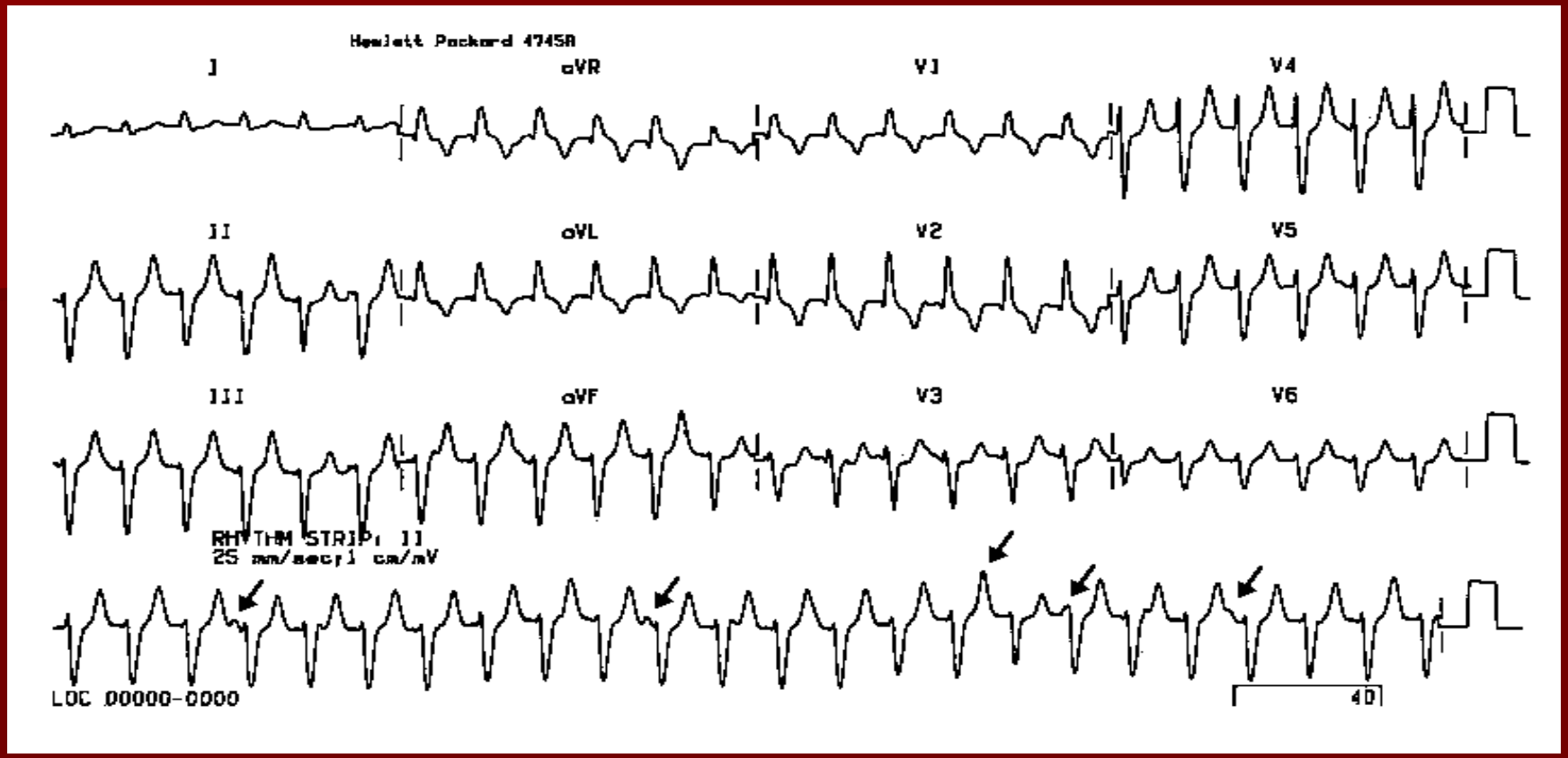


- Torsades de pointes - particular type of PMVT assoc with long QT syndrome
- Usually nonsustained (I_{Kr} ?)
- Type IA, III antiarrhythmics, TCA, Emycin, pentamidine, azole antifungals, electrolytes or congenital
- Triggered activity
- MgSO4, temp pacing, IB’s, DC offending agent, correct electrolytes

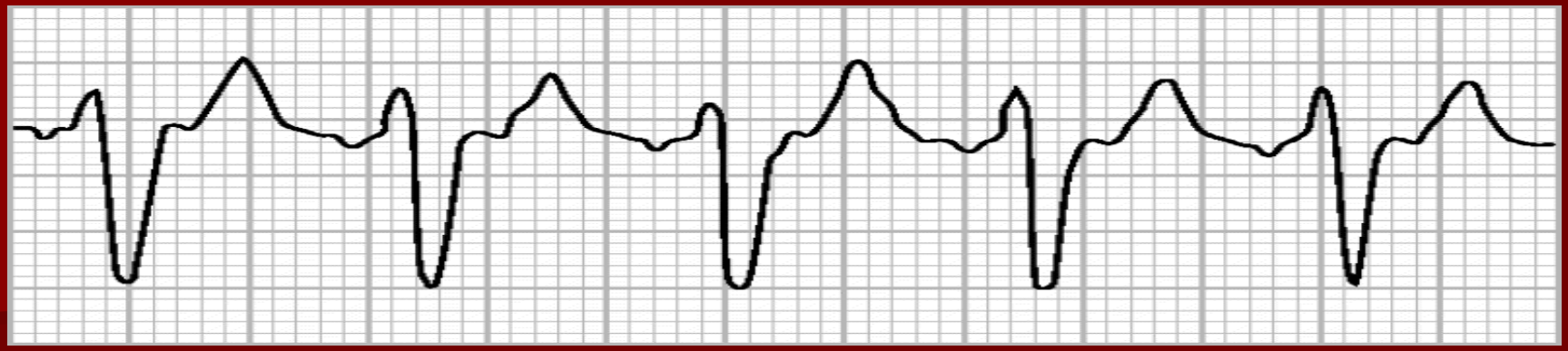


- PMVT
- Often ischemically mediated
- Triggered activity/abnormal automaticity/reentry?
- Defibrillation
- Correct underlying ischemia
- Beta-blockers, lidocaine, amiodarone

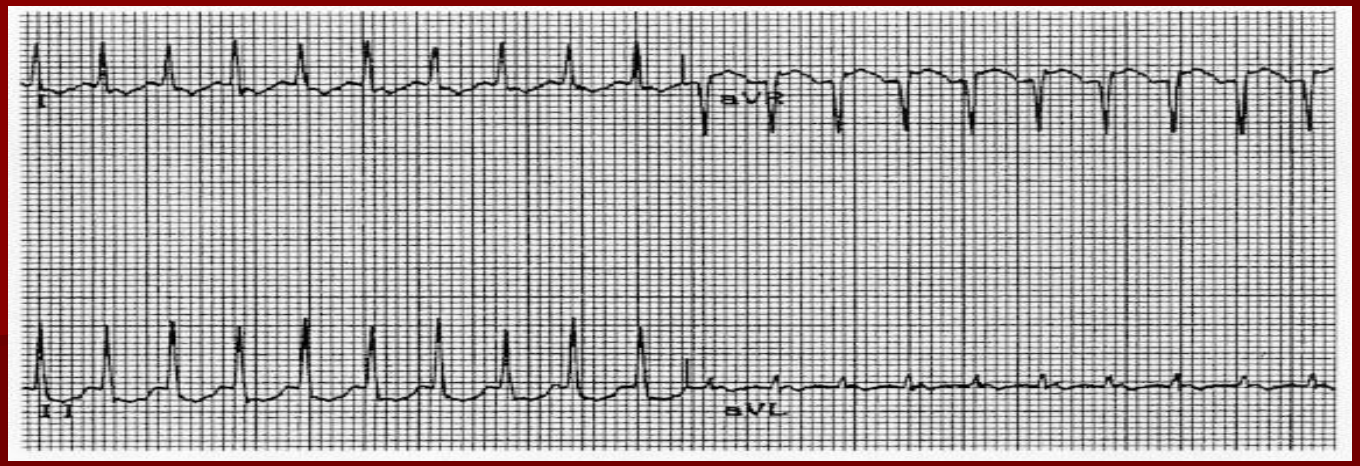

Unconfirmed



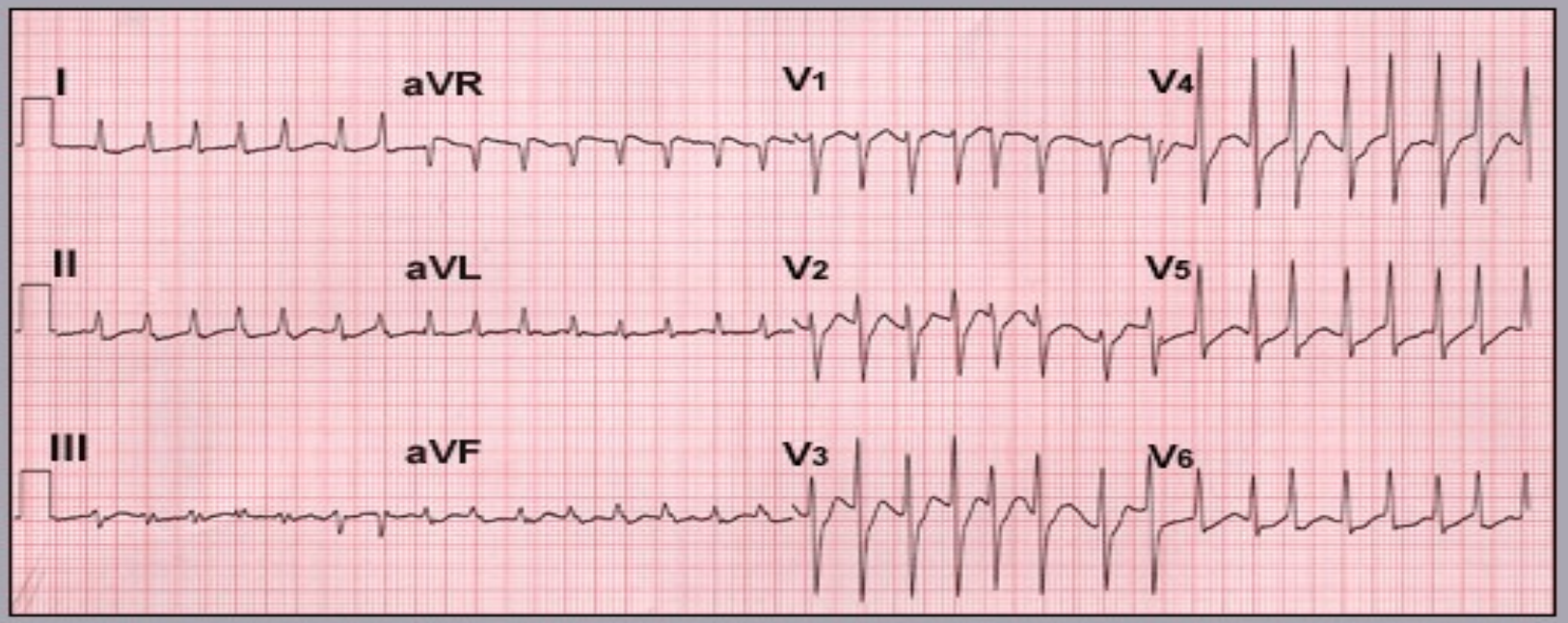
- Ventricular tachycardia (AV dissociation)
- Reentry
- DCCV, Amio, Lidocaine



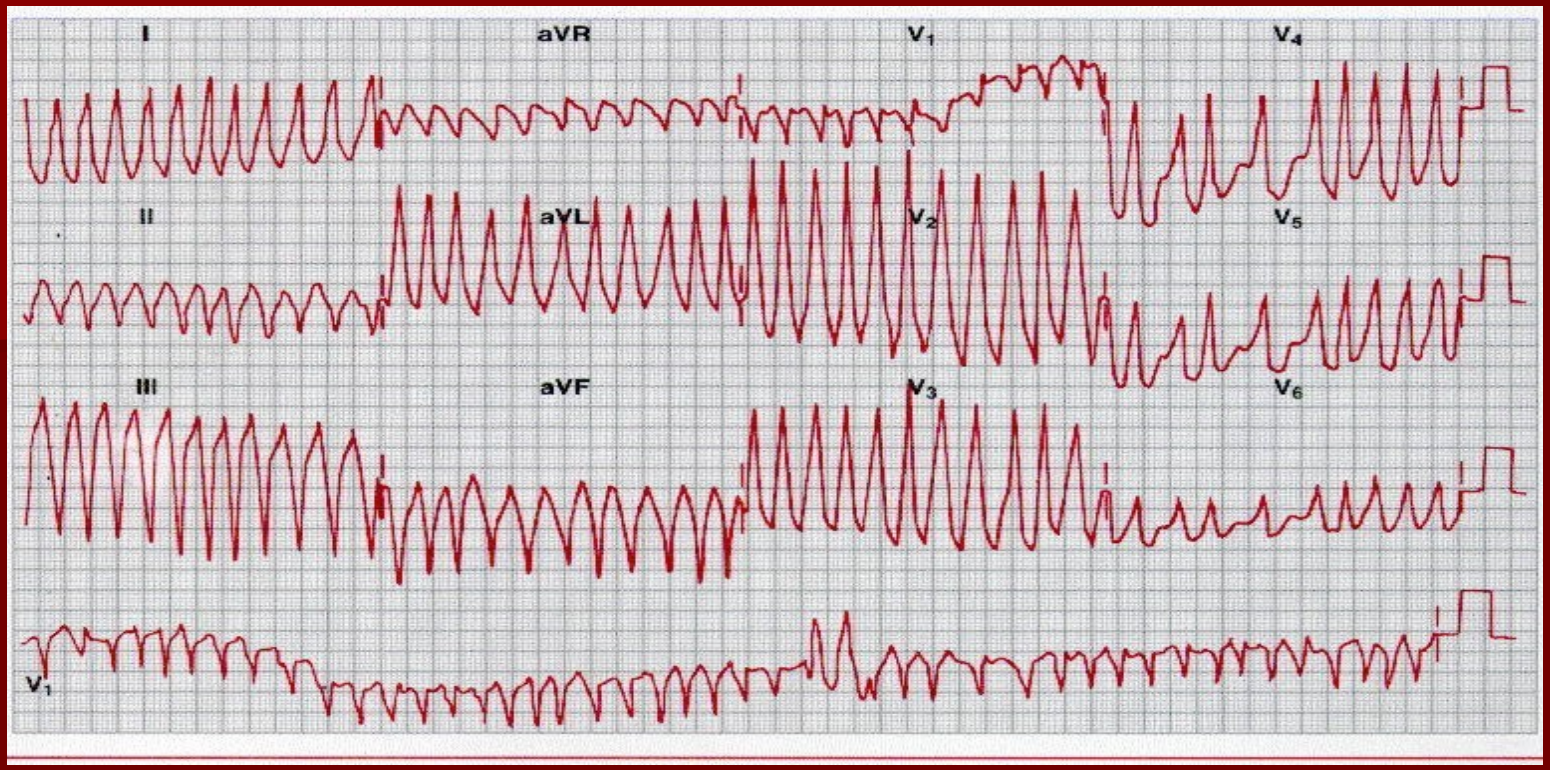
- Atrial tachycardia with block
- Digoxin toxicity- inc automaticity/DAD’s?
- Replace electrolytes, observation, IB’s, Digoxin antibodies
- Avoid DCCV



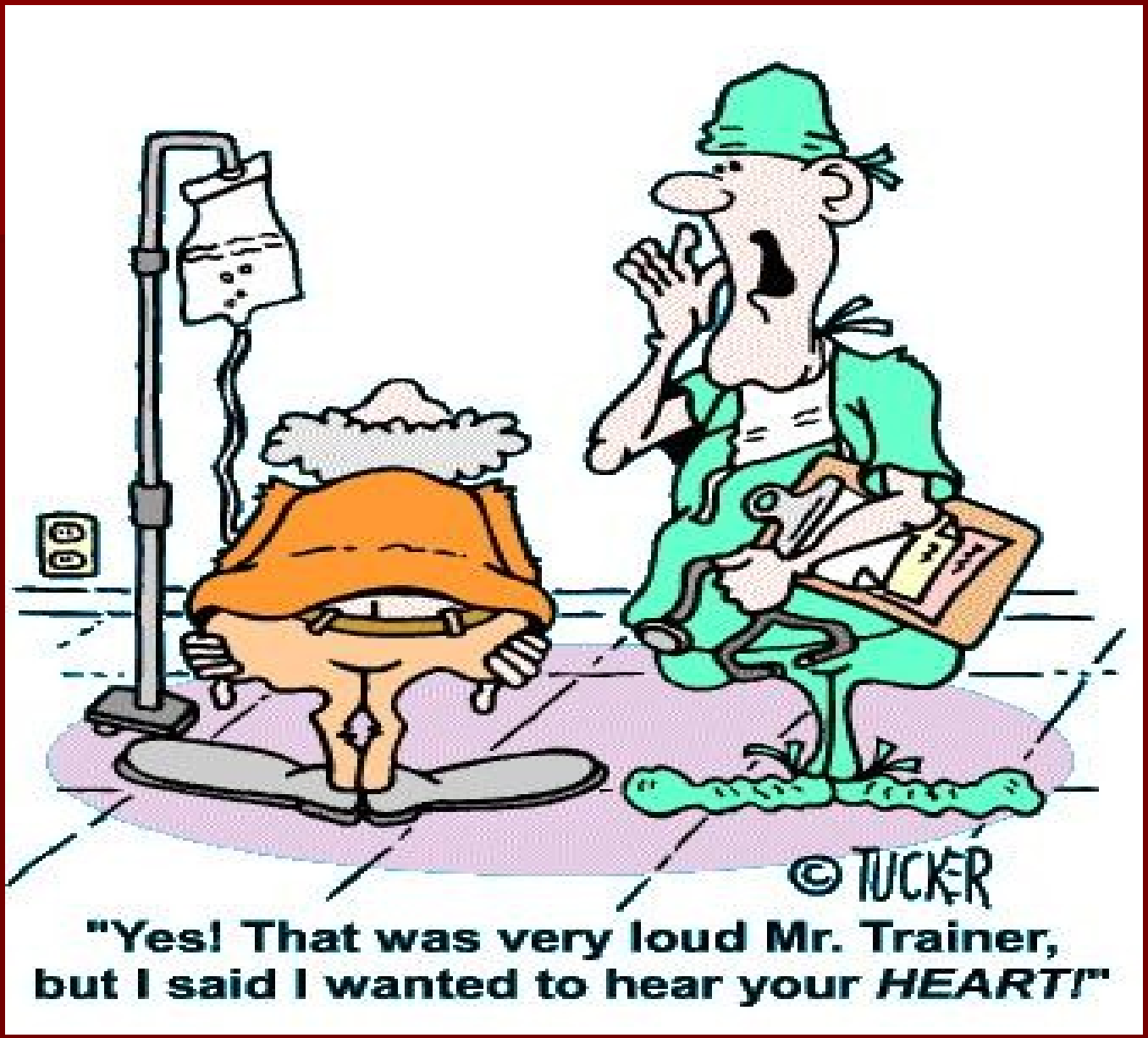
- PSVT
- AVNRT/AVRT reentry, Atrial tach abnormal automaticity/reentry?
- Adenosine for AVNRT/AVRT
- Beta-blockers for atrial tachycardia



- Atrial fib, rapid ventricular response
- Reentry
- Slow ventricular response
- Beta-blocker, diltiazem



- Afib with ventricular preexcitation
- Reentry
- Slow response
- Procainamide/Ibutilide


© TUCKER
"Yes! That was very loud Mr. Trainer,
but I said I wanted to hear your HEART!"